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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/594,170	07/20/2007	Gen-Sheng Feng	BURNHAM.010NP	7231

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EXAMINER	
BERTOGLIO, VALARIE E	

ART UNIT	PAPER NUMBER
1632	

NOTIFICATION DATE	DELIVERY MODE
08/19/2010	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/594,170	FENG ET AL.	
	Examiner	Art Unit	
	Valarie Bertoglio	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 June 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *7-12,14 and 26-43* is/are pending in the application.

4a) Of the above claim(s) *7-12 and 14* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *26-43* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *25 September 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *12/2007*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's election without traverse of Group III in the reply filed on 06/07/2010 is acknowledged. Claims 7-12 and 14 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 06/07/2010.

Claims 1-6, 13 and 15-25 are cancelled. Claims 7-12 and 14 are withdrawn. Claims 26-43 are under consideration.

Enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 26-32 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a genetically modified mouse whose genome comprises a $Shp2^{flox}$ allele wherein the Shp2 gene is functionally disrupted in CamK2a-expressing cells such that no Shp2 is expressed in said cells and wherein said mouse exhibits increased body weight, early-onset obesity, and resistance to leptin, does not reasonably provide enablement for the full scope of the claims. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, are set forth in *In re Wands*, 8 USPQ2d 1400, at 1404 (CAFC 1988). These factors include: (1) the nature of the invention, (2) the state of the prior art, (3) the relative level of skill of those in the art, (4) the predictability of the art, (5)

the breadth of the claims, (6) the amount of direction or guidance presented, (7) the presence or absence of working examples, and (8) the quantity of experimentation necessary (MPEP 2164.01(a)).

The claims are directed to genetically modified mouse comprising a disrupted Shp2 gene wherein said mouse is homozygous for said disrupted gene and exhibits increased body weight in comparison to a wildtype control mouse. Dependent claims recite additional phenotypes. Claim 27 limits the disruption to the forebrain (i.e. cells of the forebrain). The claims encompass mice that have a disruption in the Shp2 gene in all cells of the mouse or in cells other than cells of the forebrain.

The specification teaches a conditional knockout of the Shp2 gene in CamK2a-expressing forebrain cells (CaSKO mouse). The specification teaches use of a homologous recombination construct with loxP sites flanking exon 4 of the Shp2 gene to generate a line of mice ($Shp2^{flox}$) that, when crossed to a Cre-expressing line, will lose expression of Shp2 in Cre-expressing cells. Cre-mediated recombination results in deletion of exon4 and a frameshift that results to premature truncation. The specification teaches crossing the $Shp2^{flox}$ mouse to a mouse where the promoter driving expression of a Cre recombinase transgene is the CaMK2a promoter. The CaMK2a promoter drives expression only in the neurons of the hippocampus (see Reece 2004, page 388, provided herewith). The pattern of expression of the Cre recombinase determines which cell will lose expression of Shp2, which will then determine the phenotype of the mouse. The specification has taught only the CaSKO mouse lacking Shp2 in CaMK2a expressing cells. The specification has not taught other mice encompassed by the claims.

The art has demonstrated other conditional knockouts of the Shp2 gene wherein loss of Shp2 expression from other cells types, resulting from use of different promoters driving Cre

expression, leads to phenotypes other than those claimed and disclosed in the specification (for example, see Grossman, PNAS. 2009, 106:16704-16709; Nakamura, PNAS, 2009, 106:11270-11275). The art has also demonstrated that a non-conditional knockout of Shp2 in all cells of a mouse is embryonic lethal (Saxton, 1997, EMBO J, 16:2352-2364). Therefore, the specification enables making only a mouse lacking Shp2 expression in CaMK2a-expressing cells with the claimed phenotypes. The phenotypes of other Shp2-disrupted mice would differ from those of the mice disclosed in the specification for the CaSKO mouse and therefore, the specification fails to enable those other mice encompassed by the claims.

Therefore, because the specification only teaches use of the CaMK2a promoter to drive Cre-mediated recombination to knockout the Shp2 gene in forebrain cells to obtain a mouse with the claimed phenotypes, and because loss of Shp2 activity in other cells results in other phenotypes, including lethality, the specification fails to enable any mouse other than a genetically modified mouse whose genome comprises a $Shp2^{flox}$ allele wherein the Shp2 gene is functionally disrupted in CamK2a-expressing cells such that no Shp2 is expressed in said cells and wherein said mouse exhibits increased body weight, early-onset obesity, and resistance to leptin.

Claims 33-43 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The method claims, claims 33-43, are drawn to use of the CaSKO mouse to screen for compounds to prevent or ameliorate obesity are not enabled. The specification provides guidance, at length, relevant to *in vitro* screens designed to isolate Shp2 modulators as potential treatments for obesity. The specification also discusses *in vivo* testing using obese animals other than Shp2-disrupted mice (paragraph 126-127). The specification does not discuss use of Shp2-disrupted mice in a screen as claimed and one of skill in the art would not know how to carry out such a screen. The claims require determining the effect of a test compound on mice with a disruption in the Shp2 gene but do not recite how such determination is carried out. At best, the specification at paragraph 22, in reference to generic screening methods, states that "The compound is determined to treat, stabilize, or prevent a higher than desired total body weight or a higher than desired percentage of body fat if the compound increases Shp2 activity or binds to a Shp2 binding site on the leptin receptor." It is not clear how that can occur in a Shp2-disrupted mouse if Shp2 protein is not present.

Claims 36 and 37 recite that the test compound decreases Shp2 activity in neurons of the genetically modified mouse. These claims are not enabled because if the mouse lacks Shp2 expression the test compound cannot be acting by decreasing Shp2 expression. A genetic-based loss in Shp2 expression leads to increased body weight. Thus, it does not follow that a compound leading to a decreased weight (claim 33) would result from a test compound decreasing Shp2 activity. A compound-based decrease in Shp2 would be expected to mimic the genetic-based effect.

Claims 33-43 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

> *Vas-Cath Inc. v. Mahurkar*, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116).

The method claims, claims 33-43, are drawn to use of the CaSKO mouse to screen for compounds to prevent or ameliorate obesity are not enabled. The specification provides guidance, at length, relevant to *in vitro* screens designed to isolate Shp2 modulators as potential treatments for obesity. However, the specification fails to disclose use of the claimed conditional Shp2 disrupted mouse in an in vivo screen.

Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 36-37 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 36 and 37 recite that the test compound decreases Shp2 activity in neurons of the genetically modified mouse. These claims are not clear because if the mouse lacks Shp2 expression the test compound cannot be acting by decreasing Shp2 expression. A genetic-based loss in Shp2 expression leads to increased body weight. Thus, it does not follow that a compound leading to a decreased weight (claim 33) would result from a test compound decreasing Shp2 activity. A compound-based decrease in Shp2 would be expected to mimic the genetic-based effect.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Valarie Bertoglio whose telephone number is (571) 272-0725. The examiner can normally be reached on Mon-Thurs 5:30-4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on (571) 272-4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Valarie Bertoglio/
Primary Examiner, Art Unit 1632